

## **REMARKS**

These remarks are in response to the Office Action mailed December 31, 2010. Support for the amendments can be found throughout the specification and claims as filed. For example, support can be found at paragraph [0040] and [0092] of U.S. Patent Publication No. 20020127697 A1. No new matter is believed to have been introduced.

### **I. REJECTION UNDER 35 U.S.C. §103**

Claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121 stands rejected under 35 U.S.C. §103 as allegedly unpatentable over Ram *et al.* (Cancer Research, 1993, 53:83-88) in view of each of Martuza *et a.* (U.S. Patent No. 5,585,096), Murakami *et al.*, (Gene, 1997, 202:23-29) and Sobol *et al.* (U.S. Patent No. 5,674,486).

Claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-121 are rejected as allegedly unpatentable over Ram *et al.* (Cancer Research, 1993, 53:83-88) in view of each of Martuza *et a.* (U.S. Patent No. 5,585,096), Murakami *et al.*, (Gene, 1997, 202:23-29) and Sobol *et al.* (U.S. Patent No. 5,674,486) and further in view of Douar *et al.* (Gene Ther, 3:780-796, 1996), which is further combined to overcome certain deficiencies in the primary set of references.

Claims 41, 43-45, 49-51, 56, 58, 59, 61, 66, 70, 71, 73, 75, 78-80, 87-92, 97-102, 105-110, 115-119, and 121 are rejected as allegedly unpatentable over Ram *et al.* (Cancer Research, 1993, 53:83-88) in view of each of Martuza *et a.* (U.S. Patent No. 5,585,096), Murakami *et al.*, (Gene, 1997, 202:23-29) and Sobol *et al.* (U.S. Patent No. 5,674,486) as above and further combined with Vile *et al.* (Virology, 214:307-313, 1995) and Yan *et al.* (Prostrate, 32:129-139, 1997), which are further combined to overcome certain deficiencies in the primary set of references.

Claims 41, 43-45, 49-51, 56, 58, 61, 63-73, 75, 78-82, 87-119, and 121 are rejected as allegedly unpatentable over Ram *et al.* (Cancer Research, 1993, 53:83-88) in view of each of Martuza *et a.* (U.S. Patent No. 5,585,096), Murakami *et al.*, (Gene, 1997, 202:23-29) and Sobol *et al.* (U.S. Patent No. 5,674,486) as above, and further combined with Vile *et al.* (Virology, 214:307-313, 1995) and Kasahara *et al.*

(Science, 266:1373-1376, 1994), to overcome certain deficiencies in the primary set of references.

Applicants respectfully traverse these rejections as set forth previously in the Response filed August 2008 and September 2009, which is incorporated herein by reference.

A *prima facie* case of obviousness requires that the references when combined **MUST** teach or suggest each and every element of Applicants' claimed invention and **MUST** demonstrate a reasonable expectation of success. Applicants' independent claims require at a minimum "a replication competent retrovirus that infects mammalian cells . . ." and comprises an IRES cassette. The combination of references, particularly Ram et al., Martuza et al. and Murakami et al. fail to teach or suggest Applicants' claimed invention as discussed more fully below, the combination fails to teach or suggest each and every element of Applicants' invention. The table immediately below provides examples of the teachings of the individual references as well as exemplary deficiencies:

Reference	Teaching/suggestion	Does <u>not</u> teach or suggest
Ram et al.	<u>Cell</u> delivery; defective retroviral DNA in cells used for delivery	Replication competent oncoretroviral nucleic acids; recombinant replication competent oncovirus that infect mammalian cells; delivery of oncovirus to mammals; IRES cassette; location of IRES cassette
Martuza et al.	defective DNA lytic virus	Replication competent oncoretroviral nucleic acids; recombinant replication competent oncovirus that infect mammalian cells; delivery of oncovirus to mammals; IRES cassette; location of IRES cassette
Murakami et al.	Avian Rous Sarcoma Virus; IRES Cassette	Replication competent retroviral nucleic acids the propagate in mammalian cells; recombinant replication competent oncovirus that infect mammalian cells; delivery of oncoviruses to mammals

The Examiner will note that the exemplary table above demonstrates that each of these references fail to teach particular elements of the claimed invention that are consistent across all the references and thus the teachings are lacking when the references are combined. The combination fails to teach or suggest, for example, recombinant replication competent oncoretroviral nucleic acids; recombinant replication competent oncoviruses that infect mammalian cells; and delivery of such recombinant replication competent oncovirus to mammals to treat cell proliferative disorders.

Furthermore, the combination of references do not teach or suggest any reasonable expectation of success of recombinantly modifying a replication competent mammalian oncovirus such that it can infect a mammalian cell and treat a cell proliferative disorder. For example, the Examiner recognizes that defective viruses do not work effectively; DNA lytic viruses are unrelated to retroviruses and thus do not function as retroviruses; and RSV does not infect mammalian cells (Ram et al., Martuza et al. and Murakami et al., respectively). Accordingly, there could be no expectation of success from the combination of the references.

For any of these reasons, the aforementioned feature of the independent claims cannot reasonable be said to be present in the asserted combination. The references are discussed in more detail below, however, the Examiner is reminded that failure of an asserted combination to teach or suggest each and every feature of a claim remains fatal to an obviousness rejection under 35 U.S.C. § 103, and failure to demonstrate a reasonable expectation of suggest also remains fatal to an obviousness rejection despite any recent revision to the Manual of Patent Examining Procedure (MPEP).

Section 2143.03 of the MPEP requires the "consideration" of every claim feature in an obviousness determination. To render the independent claims unpatentable, however, the Office must do more than merely "consider" each and every feature for this claim. Instead, the asserted combination of the references to Ram et al., Martuza et al. and Murakami et al. must also teach or suggest *each and every claim feature*. See *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (emphasis added) (to establish *prima facie* obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art). Indeed, as the

Board of Patent Appeal and Interferences has recently confirmed, a proper obviousness determination requires that an Examiner make “a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art.” See *In re Wada and Murphy*, Appeal 2007-3733, citing *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). Further, the necessary presence of all claim features is axiomatic, since the Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including ... ascertaining the differences between *the claimed invention* and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) (emphasis added). Indeed, Applicant submits that this is why the MPEP instructs Examiners to conduct an art search that covers “the invention *as described and claimed*.” (emphasis added). Lastly, Applicants respectfully direct attention to MPEP § 2143, the instructions of which buttress the conclusion that obviousness requires at least a suggestion of all of the features of a claim, since the Supreme Court in *KSR Int'l v. Teleflex Inc.* stated that “there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Furthermore, as demonstrated to the Examiner and the Examiner's Supervisor during the in-person interview last year that claimed invention demonstrates unpredictable results including long term propagation and vector stability. These cannot be merely dismissed as being unimportant since they provide true benefit to the methods of treatment described and claimed by the present disclosure and provide a foundation for successful gene therapy.

In sum, it remains well-settled law that obviousness requires at least a suggestion of all of the features in a claim. See *In re Wada and Murphy*, citing *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). It is also well-settled that there must be some reasonable expectation of success. Applicants have demonstrated that not just any location of an IRES cassette in an MLV virus is capable of providing long term propagation and stability.

As previously demonstrated by affidavit from Dr. Chiang, the advances made by Dr. Kasahara and colleagues in 1998 were opposite to the direction the field was

taking. There was incredible concern about the use of replication competent retroviruses as well as defective retroviruses.

Furthermore, MLV viruses were known to be unstable to exogenous gene insertions and would lose expression after only a single or few rounds of replication. The literature shows insertional cassettes in retroviruses in LTR's and outside LTR's were generally lost over a short period of time (as demonstrated to the Examiner in the in-person interview of last year). In addition, part of the reason defective MLV vectors were used is because the removal of the genes necessary for replication increased the "loading capacity" of the vector and increased stability of the resulting cassette. It was not until Dr. Kasahara's invention that the use, stability and benefits of a replication competent retrovirus with an IRES cassette located outside the LTRs and following the *env* gene was demonstrated. This is evidenced again by the large number of references in the field discussing the advantages of Dr. Kasahara's invention.

The combination of reference provided by the Patent Office requires so many variations and assumptions that were beyond the scope of understanding in the art at the time of the invention. In other words, the combination arrived at by the Patent Office is the result of hindsight reconstruction utilizing references that one of skill in the art would ***not*** consider relevant to the invention. For example, one of skill in the art would not combine cell transplantation vectors (Ram et al.), with DNA lytic viruses (Martuza et al.), with avian viruses (Murakami et al.) to arrive at Applicants' claimed invention.

First, Ram et al. is hardly relevant to Applicants' claimed invention. Ram et al. is not directed to viral delivery but rather to delivery of cells. In addition, Ram et al. utilizes cells that comprise a gutted retroviral genome. In other words the "vector" of Ram et al. is the cell itself comprising portions of a retroviral genome. The Ram et al. reference is so far removed from Applicants' invention as to have little bearing or overlapping subject matter; in fact not a single element of Applicants' claimed invention can be found in the Ram et al. reference. The Patent Office also cites to Stull et al. (U.S. Patent No. 6,322,969) as teaching replication competent MLV vectors with IRES-transgene cassettes introduced 3' to ENV (see, page 21 of the Office Action). Stull et al. do not teach any such thing. Stull et al. teach a defective

retroviral vector, the standard in the art in the 1990's.

In fact, none of the references cited by the Patent Office teach or suggest a replication competent mammalian oncoretrovirus. The Patent Office mistakenly alleges, “. . .at the time of filing, the advantages of using replication competent retroviruses for cancer treatment was taught by the prior art. For example, Martuza et al. . . .” (see, e.g., the Office Action at page 4, 5 lines from the bottom). Martuza et al. do not teach a retrovirus, rather Martuza et al. teach a lytic virus, HSV.

At the time Martuza et al. was filed there were efforts to make HSV (a lytic DNA viruses) more replication competent; Martuza et al. is an examples of these efforts. In other words, prior HSV vectors were attenuated, some were so attenuated as to lose functionality. What Martuza et al. did was to attenuate HSV in a different way to make it more effective. Thus, when Martuza et al. is discussing replication competent viruses, Martuza et al. is focused on HSV (i.e., DNA lytic viruses), not retroviruses (see, e.g., column 2, lines 2-7; and column 3, lines 33-39). One of skill in the art would not consider the teachings of defective lytic viruses, or attenuated lytic viruses to be of use in the development of replication competent retroviruses. Accordingly, the Examiner is misconstruing the reference to provide a motivation where there is no motivation.

Herpes Simplex Virus (as described in Martuza et al.) is a complex DNA virus having a lytic life-cycle. Again, this reference has little bearing on the invention at hand. HSV viruses are simply a different organism having a different life cycle and do not behave like retroviruses. The HSV genome differs not only in the type of nucleic acid (DNA vs. RNA), but also in the type of genes, size and structure. In addition, the genome itself remains episomal, unlike retroviruses which are incorporated into the genome. It is also recognized that HSV infections cause an immune response and thus are detrimental to genetic therapy. One would not want to induce an immune reaction since such a reaction would reduce the spread of the virus to cancerous cells. One of skill in the art would not consider HSV vectors to be relevant to retroviral vector development because of these fundamental differences in structure and life-cycle.

The Patent Office suggests that one of skill in the art would combine HSV vectors of Martuza et al. with the defective MLV of Ram et al. to obtain replication

competent retroviral vectors for gene therapy. This could not be further from the facts. The genomes and life-cycles of HSV and MLV are so different that one of skill in the art would not combine the teachings as suggested by the Patent Office. More importantly, however, is that Martuza et al. actually teach a defective or attenuated HSV (see Figure 1 and column 2, lines 40-55 of Martuza et al.), thus, what the Patent Office is doing is combining two defective viral systems to allegedly arrive at a replication competent retrovirus. The combination of the references could not result in a replication competent retrovirus as suggested by the Patent Office. The combination of the references teach at most a defective oncolytic retrovirus. Oncolytic retroviruses do not exist, in fact an important aspect of the retrovirus is that it does not lyse the cell.

The Patent Office then proceeds to combine the foregoing references with Murakami et al. Again, Murakami et al. is directed to yet another species of virus. Murakami et al. uses Rous Sarcoma Virus (RSV). RSV is recognized to have a large gene (*i.e.*, *src*) that can be readily removed and replaced without changing the viral life cycle. In fact, the reason that this viral vector has been so widely used in research is specifically because of the flexibility of the replaceable *src* gene. There could be no predictability of using this same structure in MLV because MLV does not have the replaceable *src* gene. In fact, Oh et al. (J. of Virol., 76(4):1762-1768, 2002) makes this point very clear at page 1762, column 1, paragraph 2. In that paragraph, the author clearly indicates that most retroviral genomes cannot accommodate the insertion of a significant amount of additional genetic information but for one "exception", that exception being RSV. Accordingly, there could be no expectation that inserting an IRES with a heterologous gene into MLV would function. Furthermore, RSV is incapable of infecting mammalian subjects and thus one of skill in the art would not consider the teachings of Murakami et al. as being relevant to treating a mammal.

Thus, the combination of Ram et al., Martuza et al. and Murakami et al. leads at most to a defective oncolytic virus that infects avian cells. The combination of references truly fails to teach or suggest a method of treating a cell proliferative disorder using a recombinant replication competent oncoretrovirus or a polynucleotide thereof.

The addition of Sobol et al., Daur et al. or Kasahara et al. do not remedy the fundamental deficiencies of the combination of Ram et al., Martuza et al. and Murakami et al.

For at least the foregoing reasons, the pending claims are novel and non-obvious over the cited reference. Accordingly, Applicants respectfully request withdrawal of this rejection.

For at least the foregoing, the Applicant submits that the claimed invention is patentable and request reconsideration and notice of such allowable subject matter.

The Director is authorized to charge any required fee or credit any overpayment to Deposit Account Number 50-4586, please reference the attorney docket number above.

The Examiner is invited to contact the undersigned at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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